PSEHB/MDED Notification No. 0831-11
August 31, 2020

To: Directors of Prefectural Health Departments (Bureaus)

Director of Medical Device Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Points to Consider for Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc.

Handling of reports of malfunctions, etc. in clinical trials related to processed cells, etc. has been shown in "Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc." (PFSB Notification No. 1002-23 of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 2, 2014) and "Points to Consider for Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc." (PFSB/ELD/OMDE Notification No. 1002-1 of the Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare [in charge of evaluation and licensing of medical devices/regenerative medical products], dated October 2, 2014).

With the enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 63 of 2019) and the Ministerial Ordinance on the Development of Related Ministerial Ordinances in Accordance with Enforcement of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance No. 155 of Ministry of Health, Labour and Welfare in 2020), handling of reporting of malfunctions, etc. in clinical trials of processed cells, etc. based on Article 275-3 of Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ministry of Health and Welfare Ordinance No. 1 of 1961; hereinafter referred to as "Regulation") after the amendment by the above ministerial ordinance has been shown in "Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc." (PSEHB Notification No. 0831-10 of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated August 31, 2020; hereinafter referred to as "Director-General Notification"). The reports of malfunctions, etc. in clinical trials of processed cells, etc. will be handled as shown in the attachment in addition to the Director-General Notification. Please inform related businesses and medical institutions, etc. in your jurisdiction.

With the application of this notification, the "Points to Consider for Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc." (PFSB/ELD/OMDE Notification No. 1002-1 of the Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare [in charge of evaluation and licensing of medical devices/regenerative medical products], dated October 2, 2014) shall be abolished as of August 31, 2022.

Attachment

Points to Consider for Preparation of Reports by Sponsors and Sponsor-Investigators of Clinical Trials on Processed Cells, etc.

1 General considerations

(1) The reports of malfunctions, etc. in clinical trials based on the provisions of Article 275-3, Paragraphs 1, 2, and 4 of the Regulation shall be submitted in CD-R or DVD-R (hereinafter referred to as the "electronic media") in which the content of reports is recorded electromagnetically and the printed documents including the content to the Review Planning Division, Office of Review Management, Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA"), in principle. The paper size used for the reports should be Japan Industrial Standard A4. The content shall be clearly written in block style using ink, etc. The software and entry manual for preparation of electronic files are available on the PMDA website.
(https://www.pmda.go.jp/review-services/trials/0010.html) (Japanese only)

(2) When not all the required information can be entered in the specified column, enter "as per appendix ( )" in the column and attach the appendix.

(3) When entering dates in each column, use the Western calendar.

(4) If an appropriate Japanese name cannot be found in the medical dictionary, etc., write the name of malfunction/adverse reaction in overseas information in the original language without making extra efforts to translate it, or enter the original language in parentheses following the Japanese translation.

(5) Be sure to enter the reporter's address (the address of the office that has main functions), name, date of report, and the name of the Chief Executive of Pharmaceuticals and Medical Devices Agency. If the reporter is a corporation, enter its name and the name of the representative.

2 How to fill out the Study Product Malfunction/Infection Case Report Form (Attached Form 1 of the Director-General Notification)

When multiple study products are suspected products, enter the information on the multiple study products in one report to prepare one report for one case.

(1) Management information

1) Column for "Control number"

A Leave the column for "Identification number" blank for the first report. Enter the identification number assigned by PMDA in the second and subsequent reports.

B In the column for "Number of reports to PMDA," enter the number of reports to PMDA.

C For the columns for “Report category,” “Report type,” and “Site of occurrence of malfunction, etc.,” make sure to select an option and circle it. If the “Site of occurrence of malfunction, etc.” is a foreign country, enter the name of the country where the malfunction occurred.

2) In the column for “Date on which the first report was received,” the reporter shall make sure to enter the date on which the reporter learned the occurrence of the malfunction/infection concerned or the health damage in the subject, etc. due to the occurrence of the malfunction (hereinafter referred to as “malfunction, etc.”). Note that it is not the date on which the reporter judges it necessary to make a report of malfunctions, etc. in clinical trials, regardless of the division of the reporter who obtained the information.

3) In the column for “Date of most recent information,” enter the date on which the latest information on the report concerned is obtained.

4) In the column for “Scheduled date of next report,” enter the scheduled date of the additional report, for reports for which sufficient information, etc. have not been obtained at the time of the present report and an additional report needs to be made. In principle, the scheduled date of next report shall be the date on which the same number of days selected in the “Report category” of the “Control number” column has elapsed from the day after the submission of the present report.

5) In the columns for “Status of malfunction of investigational product” and “Status of health damage in subjects, etc.,” be sure to select one option among three and enter or circle it. If there are multiple study products, select “Yes” if a malfunction subject to reporting has occurred with any of the study products.

6) For the column for “Contact information of the person in charge,” be sure to fill out the “Name of the person in charge,” “Name of corporation,” “Department,” “Address,” “Tel,” “Fax,” and “E-mail” columns. For reports of malfunctions, etc. in clinical trials by sponsor-investigators, enter the name of the institution in the “Name of corporation” column.

(2) Information on the subject, etc.

1) Enter initials in Roman characters (half width) in the column for “Abbreviated name of the subject, etc.” The subject identification code of the clinical trial may be entered. Leave the column blank if it is unknown or there is no information.

2) Enter the age at the time of the occurrence of the malfunction, etc. in the column for “Age.” If the accurate age cannot be confirmed, “under 10 years,” “in 60s,” “child,” “elderly,” etc. may be entered. Leave the column blank if it is unknown or there is no information.

3) For the “Sex” column, select one of two choices and circle it. Leave the column blank if it is unknown or there is no information.

4) Enter the body weight at the time of the occurrence of the malfunction, etc. in the column for “Body weight.” Leave the column blank if it is unknown or there is no information.

5) Enter the height at the time of the occurrence of the malfunction, etc. in the column for “Height.” Leave the column blank if it is unknown or there is no information.

6) Column for “Status of the subject, etc. at the time of occurrence of malfunction, etc.”

A In the column for “malfunction,” enter all the malfunctions that occurred. When reporting multiple malfunctions, enter the “Name of malfunction,” “Known or unknown,” and “Date of occurrence” repeatedly for each malfunction. For the “Known or unknown” column, make sure to select one and circle it. If there are malfunctions in multiple study products, enter supplemental remarks, etc. in parentheses in the column for the names of malfunctions so that study products can be distinguished.

B In the column for “Status of health damage in subject,” enter all adverse events and infections that occurred. When reporting multiple adverse events and infections, enter the “Name of adverse event/infection,” “Known or unknown,” “Onset date,” “End date,” “Seriousness,” “Outcome,” and “Causality assessment” repeatedly for each adverse event or infection.

(a) For the “Known or unknown” column, make sure to select one and circle it. If there are multiple suspected products, select “Known” if the event or infection is known with all suspected products.

(b) For the column for “Seriousness,” select and enter one from “Results in death,” “Results in life-threatening disease or disability,” “Requiring hospitalization or prolongation of existing hospitalization,” “Results in permanent disability of the structure or functions of the human body,” “Causes congenital anomaly or fetal death or incapacity,” or “Other medically important conditions.”

Each option refers to the following.

- “Results in death” means “death” specified in Article 275-3, Paragraph 1, Item 1, (a) and Item 2, (b), and Paragraph 2, Item 1, (a) and Item 2, (b) of the Regulation.
- “Results in life-threatening disease or disability” means “cases that may result in death” specified in Article 275-3, Paragraph 1, Item 1, (b) and Item 2, (b), and Paragraph 2, Item 1, (b) and Item 2, (b) of the Regulation.
- “Requiring hospitalization or prolongation of existing hospitalization” means “cases requiring hospitalization in a hospital or clinic or prolongation of hospitalization period for treatment” specified in Article 275-3, Paragraph 1, Item 2, (a), (1) and Paragraph 2, Item 2, (a), (1) of the Regulation.
- “Results in permanent disability of the structure or functions of the human body” means “disability" specified in Article 275-3, Paragraph 1, Item 2, (a), (2) and Paragraph 2, Item 2, (a), (2) of the Regulation.

- “Causes congenital anomaly or fetal death or incapacity” means “a congenital disease or abnormality in later generations” specified in Article 275-3, Paragraph 1, Item 2, (a), (5) and Paragraph 2, Item 2, (a), (5) of the Regulation.
- “Other medically important conditions” means “cases that may result in disability” specified in Article 275-3, Paragraph 1, Item 2, (a), (3) and Paragraph 2, Item 2, (a), (3) of the Regulation and “cases that are serious according to cases set forth in (1) through (3) and (a) and (b) of the previous item” specified in Article 275-3, Paragraph 1, Item 2, (a), (4) and Paragraph 2, Item 2, (a), (4), which are significant events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject, etc. or may require medical or surgical intervention to prevent the outcomes such as “Results in death, “ “Results in life-threatening disease or disability, “ “Requiring hospitalization or prolongation of existing hospitalization," "Results in permanent disability of the structure or functions of the human body," and “Causes congenital anomaly or fetal death or incapacity. “

(c) In the “Outcome“ column, select and enter one from “Recovered,” “Recovering,” “Not recovered,” “Recovered with sequelae,” “Death,” or “Unknown.”

(d) In the column for “Causality assessment,” select “Related,” “Probably related,” “Possibly related,” “Not related,” or “Unknown,” and enter the assessment by the attending physician, etc. and the reporter, respectively. If there are multiple suspected products, select the option indicating stronger causality and enter the outline of assessment of each suspected product in the free text field. Describe the assessment in detail in 4. Investigation results and actions, etc., 2) Comments of attending physician, etc. and 3) Reporter's comments.

7) In the column for “Course of occurrence status of malfunction, etc.,” describe the course before and after the occurrence of the malfunction, etc. in chronological order so that the occurrence status can be easily understood. If any adverse event has occurred in a subject, etc., the status of the adverse event and whether or not any measures were taken by the medical institution for the subject, etc. If any measures were taken, the details of the measures (including changes in clinical laboratory values, etc.) should be stated.

(3) Information on investigational product

1) In the column for “Clinical trial identification code,” enter the clinical trial identification code for the main test product entered in the clinical trial notification of the investigational product concerned.

2) In the column for “Category,” enter the category of the main test product entered in the clinical trial notification of the investigational product concerned.

3) In the column for “Generic name,” enter the generic name of the main test product written in the clinical trial notification of the investigational product concerned. Leave the column blank if there is no applicable generic name.
4) In the column for “Date of clinical trial notification,” enter the date of submission of the clinical trial notification of the investigational product concerned. If multiple notifications have been made, enter all dates of notifications.
5) In the column for “Outline of clinical trials,” briefly write the protocol identification code (protocol number) entered in the clinical trial notification for the investigational product concerned, proposed indications or performance, target disease, presence or absence of subjects using the product, etc.
6) In the column for “Details of investigational products,” enter the lot number, production number, etc. of the investigational product concerned.
7) For the “Classification” column, select one according to presence or absence of designation as a designated regenerative medical products and circle it. For investigational products not approved for marketing, select and circle one that is assumed to be applicable.
8) In the column for “Status of use of investigational product,” enter the period since the start of use.
9) For the column for “Current status of investigational product,” select one of two choices and circle it. When selecting “Product not recalled,” further select and circle one of “disposed, remaining in the body, recall planned, recall impossible.”
10) In the column for "Concomitant therapies,” enter the non-proprietary names, brand names, and names of the marketing authorization holders, etc. of concomitant drugs, etc. wherever possible so that the study products (excluding suspected products), study drug equivalents, and study device equivalents (regenerative medical products, drugs, or medical devices) that were concomitantly used can be identified.
11) In the “Remarks” column, enter the number of past incidents of the malfunction, etc. that is the same as the malfunction, etc. concerned and its frequency, precautions related to the report concerned, and descriptions in the Investigator’s Brochure and the protocol. For reports of malfunctions, etc. in clinical trials by sponsor-investigators, enter the name of the investigational product provider (for a corporation, its name and name of the representative). If the investigational product provider is a foreign manufacturer, enter the name (for a corporation, its name and name of the representative) of the foreign manufacturer in Japanese and English. In cases where the malfunction, etc. was not subject to reporting when the first report was obtained but was subject to reporting when additional information was obtained, describe this matter to that effect and the base date for reporting.

If a test product other than the main test product is a suspected product, enter the category, generic name, proposed indications or performance, target disease, presence or absence of subjects using the product, lot number, production number, etc., classification, use status, and current status of the test product concerned and the fact that it is a suspected product.

If a study product other than test products is a suspected product and the study product concerned has already been approved in Japan, enter the category, generic name, brand name, approval date, intended use (comparator or concomitant product, etc.), presence or absence of subjects using the product, lot number, production number, etc., classification, use status, and current status of the study product concerned; if the study product concerned has not been approved in Japan, enter component cells or transgenes, intended use (comparator or concomitant product, etc.), presence or absence of subjects using the product, lot number, production number, etc., classification, use status, and current status of the study product concerned. Describe also the fact that it is a suspected product. If there are any study drug equivalents and study product equivalents that correspond to suspected drugs or devices, follow the above method of description for study products.

(4) Investigation results and actions, etc.

1) In the column for "Investigation results," be sure to enter the results of analysis, evaluation, and examination of the malfunction, etc. concerned. Considering the opinion of the attending physician, etc. on the investigational (study) product concerned and scientific rationale (actual data, etc.), briefly describe the cause of the malfunction, etc. concerned, status of use by the user, possibility of occurrence of similar malfunction, etc. with the investigational (study) product concerned, possibility that the malfunction, etc. concerned may cause health damage, and views on the comments of the attending physician, etc.

2) In the column for "Comments of attending physician, etc.," describe the opinion of the attending physician, etc. regarding the diagnosis and causality assessment of the malfunction, etc. concerned or other problems considered to be related. If comments of the attending physician, etc. cannot be obtained in the case of information from abroad, report this matter to that effect.

3) In the column for "Reporter's comments," describe the view on the causal relationship as a reporter with medical discussion. Also describe the effect of the malfunction, etc. concerned on subjects, etc. (effect of the malfunction, etc. concerned on subjects, etc. who used the investigational (study) product concerned and subjects, etc. who will use the investigational (study) product in the future). If the assessment of seriousness is different between the attending physician, etc. and the reporter, write the details. In the case of information from abroad, enter the comments of the reporter in Japan, not the comments of the company overseas.

4) In the column for "Previous actions," be sure to enter the presence or absence of actions that have been taken by the reporter since obtaining the information on the malfunction, etc. concerned up to the time of reporting to prevent recurrence of similar cases or to ensure the safety of subjects, etc., and if there are such actions, describe details and reasons for the actions.

5) In the column for "Future actions," describe the actions taken based on the reporter's evaluation of the malfunction, etc. concerned and future actions, referring to the following.

A State that actions such as reporting to medical institutions, revision of the informed consent form, revision of the protocol, revision of the Investigator's Brochure, revision of the summary of approval application data (draft PRECAUTIONS, etc.), etc. have been taken or are scheduled to be taken. For reporting to medical institutions, write the means (sending of communication documents, provision of revised Investigator's Brochure, telephone communication, etc.) as well.

B In the case of information from abroad, enter the actions taken by the reporter in Japan, not the actions taken by the company overseas.

6) If a study drug equivalent or a study product equivalent is a suspected drug or a suspected device, follow the above method of description for study products.

3 How to fill out the Report on Investigation of Research Report (hereinafter referred to as "research report") of Investigational Product and Report on Investigation of Actions Overseas Including Discontinuation of Manufacturing, etc., Recall, and Disposal (hereinafter referred to as "foreign corrective action report") of Investigational Product (Attached Form 2 of the Director-General Notification)

(1) Management information

1) Column for "Control number"

A Leave the column for "Identification number" blank for the first report. Enter the identification number assigned by PMDA in the second and subsequent reports.

B In the column for "Number of reports to PMDA," enter the number of reports to PMDA.

C For the column for "Report type," make sure to select between the two and circle it.

2) In the column for "Date on which the first report was received," make sure to enter the date on which the reporter learned the information requiring submission of a research report or a foreign corrective action report. Note that the reporter who obtained the information can be from any division and that the date on which the first report was received is not the date on which the reporter judges the research report or the foreign corrective action report as necessary.

3) In the column for "Date of most recent information," enter the date on which the latest information on the report concerned is obtained.

4) In the column for "Scheduled date of next report," if sufficient information, etc. have not been obtained at the time of the present report and an additional report needs to be made, enter the scheduled date of the report. In principle, the scheduled date of the next report shall be the date within 15 days from the day after the submission of the present report.

5) In the columns for "Status of malfunction of investigational product" and "Status of health damage in subjects, etc.," be sure to select one option among the three and circle it.

6) For the column for "Contact information of the person in charge," be sure to fill out the "Name of the person in charge," "Name of corporation," "Department,"

"Address," "Tel," "Fax," and "E-mail" columns. For reports by sponsor-investigators, enter the name of the institution in the "Name of corporation" column.

(2) Information on investigational products

1) In the column for "Clinical trial identification code," enter the clinical trial identification code for the main test product entered in the clinical trial notification of the investigational product concerned.
2) In the column for "Category," enter the category of the main test product entered in the clinical trial notification of the investigational product concerned.
3) In the column for "Generic name," enter the generic name of the main test product entered in the clinical trial notification of the investigational product concerned. Leave the column blank if there is no applicable generic name.
4) In the column for "Date of clinical trial notification," enter the date of submission of the clinical trial notification of the investigational product concerned. If multiple notifications have been made, enter all dates of notifications.
5) In the column for "Outline of clinical trials," briefly write the protocol identification code (protocol number) entered in the clinical trial notification for the investigational product concerned, proposed intended use, target disease, presence or absence of subjects using the product, etc.
6) In the column for "Details of investigational products," enter the lot number, production number, etc. of the investigational product concerned.
7) For the "Classification" column, select one according to presence or absence of designation as a designated regenerative medical product and circle it. For investigational products not approved for marketing, select and circle one that is assumed to be applicable.
8) In the "Remarks" column, enter the precautions related to the research report or foreign corrective action report concerned and descriptions in the Investigator's Brochure and the protocol.

For a research report or foreign corrective action report related to a test product other than the main test product, write the matter to that effect and enter the category, generic name, proposed intended use, target disease, presence or absence of subjects using the product, lot number, production number, etc., classification, etc. of the test product concerned.

For a foreign corrective action report related to a study product other than test products (limited to the implementation of actions that prevent the occurrence or spread of public health hazards in combined use with the test products), describe the matter to that effect and, if the study product concerned has already been approved in Japan, enter the category, generic name, brand name, approval date, intended use (comparator or concomitant product, etc.), presence or absence of subjects using the product, lot number, production number, classification, etc.; if the study product concerned has not been approved in Japan, enter component cells or transgenes, intended use (comparator or concomitant product, etc.), presence or absence of subjects using the product, lot number, production number, classification, etc. of the study product concerned. For a foreign corrective action

report on a study drug equivalent or a study device equivalent (limited to the implementation of actions that prevent the occurrence or spread of public health hazards in combined use with the test products), follow the above method of description for study products.

(3) Report contents and actions, etc.

1) Column for “Details of research report or action”

A Fill out the column for “Source of research report” only for research reports so that academic journals, etc. in which the information concerned has been published can be identified.

B Fill out the column for “Country where action is taken” only for foreign corrective action reports. Enter the name of the country/region where the action that triggered the report was taken.

C Fill out the column for “Action category” only for foreign corrective action reports. Enter the specific content of the action (e.g., recall, modification related to monitoring, precautions, revision of the Investigator’s Brochure, etc.).

D In the column below the column for “Action category,” make sure to enter the summary of the content of the research report or foreign corrective action report.

2) In the column for “Previous actions,” be sure to enter the presence or absence of actions that have been taken by the reporter in Japan since obtaining the information concerned up to the time of reporting and if there are such actions, describe details of the actions and reasons for the actions.

3) In the column for “Future actions,” describe measures based on the reporter’s evaluation of the malfunction, etc. concerned and future actions, referring to the following.

A State that actions such as reporting to medical institutions, revision of the informed consent form, revision of the protocol, revision of the Investigator’s Brochure, revision of the summary of approval application data (draft PRECAUTIONS, etc.), etc. have been taken or are scheduled to be taken. For reporting to medical institutions, describe the means (sending of communication documents, provision of revised Investigator's Brochure, telephone communication, etc.) as well.

B In the case of information from abroad, enter the actions taken by the reporter in Japan, not the actions taken by the company overseas.

4 How to fill out the Investigational Product Periodic Safety Report (Attached Form 3-1 of the Director-General Notification)

(1) In the column for “Clinical trial identification code,” enter the clinical trial identification code for the main test product entered in the clinical trial notification of the investigational product concerned.

(2) In the column for “Category,” enter the category of the main test product entered in the clinical trial notification of the investigational product concerned.

(3) In the column for “Generic name,” enter the generic name of the main test product entered in the clinical trial notification of the investigational product concerned. Leave the column blank if there is no applicable generic name.
(4) In the column for “Date of the first notification,” enter the date on which the first clinical trial notification related to the investigational product concerned was submitted.
(5) In the column for "Base date for reporting,” enter the base date for the annual periodic report (hereinafter referred to as the "annual report") based on Article 275-3, Paragraph 4 of Regulation for the investigational product concerned. The base date for reporting shall be, in principle, the date of the first submission of the clinical trial notification for the investigational product concerned (for investigational products related to a drug, machine, or equipment, etc. for which clinical trial notifications were submitted on or before November 24, 2014, if a new clinical trial notification for such investigational products has been submitted on or after November 25, 2014, the base date for reporting is the date of submission of the clinical trial notification a drug, machine, or equipment, etc.). When changing the base date for reporting, consult the Review Planning Division, Office of Review Management, PMDA in advance and submit the request for change of base date for reporting. In the “Request for change of base date for reporting” (free format), enter the “clinical trial identification code,” “original base date,” “new base date,” “reasons for changing base date,” and “subsequent scheduled survey unit periods.”
(6) In the column for “Outline of clinical trials,” briefly write the protocol identification code (protocol number) entered in the clinical trial notification for the investigational product concerned, proposed indications or performance, target disease, presence or absence of subjects using the product, etc.
(7) In the column for “Details of investigational products,” enter the lot number, production number, etc. of the test product concerned.
(8) For the column for “Investigational product classification,” select presence or absence of designation as a designated regenerative medical product and circle it. For investigational products not approved for marketing, select and circle the one that is assumed to be applicable.
(9) In the column for “Reporting period,” enter the period during which malfunctions, etc. were accumulated for the report concerned.
(10) In the column for "Number of reports to PMDA,” enter the total number of submissions for the report concerned.
(11) In the column for “Information on changes in investigational product,” enter the content and reasons of the change if the investigational product has been changed during the reporting period concerned. If the investigational product has been changed for a reason related to safety measures, describe the occurrence status of malfunctions, etc. after the change.
(12) In the column for “Approval status overseas,” if the investigational product concerned has been approved overseas, enter the name of the country where the approval was granted, approval date, quantity shipped, etc. as much as possible.

(13) In the column for “Occurrence status of malfunction, etc.,” briefly describe the occurrence status of malfunctions, etc. of the study product obtained during the reporting period concerned. Attach the “List of Occurrence Status of Cases of Investigational Product Malfunctions/Infections” specified in Attached Form 3-2 of the Director-General Notification. If a malfunction, etc. in clinical trials has been reported without unblinding in a double-blind study, write the method of tabulation of cases that have not been unblinded.

(14) In the column for “Comments and safety measures based on accumulation,” describe the reporter’s opinion based on the accumulated evaluation of malfunctions, etc. during the reporting period concerned and the accumulated evaluation up to the time of the previous report. The reporter’s opinion should include the following contents.

1) The contents of new safety assurance measures taken by the reporter and future safety measures should be described.
2) Describe whether measures such as revision of the informed consent form to be provided to subjects and revision of the protocols have been taken or are scheduled to be taken, along with its reasons.
3) In the case of information from abroad, enter the actions taken by the reporter in Japan, not the actions taken by the company overseas.

(15) “Remarks” column

1) Enter name of a person in charge, name of a corporation or institution, department, address, phone number, fax number, etc. as contact information.
2) If the base date for reporting has been changed, report the matter to that effect and enter the date of submission of the request for change of the base date for reporting.
3) If the report concerned is the final report because of approval or discontinuation of development, enter the approval date or date of discontinuation of development.
4) If a test product other than the main test product is used, enter the category, generic name, proposed intended use, target disease, presence or absence of subjects using the product, lot number, production number, classification, information on changes, and approval status, etc. overseas of the test product concerned.

If a study product other than test products is used and the study product concerned has already been approved in Japan, enter the category, generic name, brand name, approval date, intended use (comparator or concomitant product, etc.), presence or absence of subjects using the product, lot number, production number, classification, and information on changes, and approval status, etc. overseas of the study product concerned; if the study product concerned has not been approved in Japan, enter component cells or transgenes, intended use (comparator or concomitant product, etc.), presence or absence of subjects using the product, lot number, production number, classification, information on changes, and approval status, etc. overseas of the study product concerned. If a study drug equivalent or a study product equivalent is used, follow the above method of description for study products.

5 How to fill out the List of Occurrence Status of Cases of Investigational Product Malfunctions/Adverse Events (Attached Form 3-2 of the Director-General Notification)

(1) Make reports by classifying the information into clinical trials in Japan, overseas clinical studies, and overseas post-marketing spontaneous reports. Of products used in other countries considered to have the same component cells or transgenes as those of the study product concerned, those not approved in other countries shall be listed in the column for overseas clinical studies, and those approved shall be listed in the column for overseas post-marketing spontaneous reports.

(2) In the column for "Approximate number of subjects, etc.," enter the number of subjects in already conducted clinical studies, approximate number of registered subjects in ongoing clinical trials, and approximate number of users overseas as much as possible for the investigational product concerned or products used overseas considered to have the same component cells or transgenes as those of the investigational product concerned.

(3) In the columns for "Type of malfunction" and "Number of malfunctions by type," enter the number of incidents of malfunctions, etc. calculated by type of the study product, type of malfunctions, etc., and type of cases, for known and unknown serious adverse events (excluding those due to the effect of infection) and observed malfunctions that may lead to serious cases (excluding those due to the effect of infection), based on Article 275-3, Paragraph 4 of the Regulation. If multiple adverse events have occurred in the same case, each adverse event shall be counted as one case subject to reporting.

(4) In the columns for "Type of infection" and "Number of infections by type," enter the number of known or unknown serious infections caused by, or suspected to have been caused by the use of the study product that is calculated by type of the study product and type of infection, based on Article 275-3, Paragraph 4 of the Regulation.

(5) In the column for "Total," enter the total from the first reporting period to the end date of the present reporting period.

(6) In the "Remarks" column, describe any reference matters such as prerequisites for counting the number of incidents.

(7) If adverse reactions or malfunctions, etc. of study drug equivalents or study device equivalents are subject to reporting, follow the above method of description for study products.

6 Other precautions

When submitting reports of malfunctions, etc. in clinical trials, pay attention to the following points.

(1) Criteria for determination of expectedness, etc.

In reports of malfunctions, etc. in clinical trials, expectedness shall be judged based on the following.

1) Expectedness shall be judged based on the malfunctions, etc. described in the Investigator's Brochure or the documents describing scientific findings

(instructions for use, academic papers, etc.) on study products (other than test products) (hereinafter referred to as “Investigator’s Brochure, etc.”), in principle.

2) An adverse reaction shall be judged as being “expected” on the day of preparation or revision of the Investigator's Brochure, etc. or the day of preparation of communication documents. Therefore, an adverse event of which medical institutions have been notified via a communication document is regarded as “expected” even if the Investigator’s Brochure has not been revised.

3) Even if the malfunction, etc. is described in the Investigator's Brochure, etc., it shall be judged “unexpected” if the occurrence tendency such as the number of cases, frequency, and conditions of occurrence is not consistent with the description.

4) For products for which clinical trials have been completed and an approval application is pending, the basis for judgment of expectedness shall be the summary of product application for the product concerned regardless of 1).

5) If any clinical trial has been continued after approval application and has been completed before the approval of the product concerned, the basis for judgment of expectedness shall be switched from the Investigator’s Brochure to the summary of product application as of the date of submission of the clinical trial completion notification for the clinical trial concerned.

6) If any clinical trial has been continued after approval application and has been completed before the approval of the product concerned, the basis for judgment of expectedness shall be switched to the Investigator’s Brochure, regardless of 5), when a clinical trial of a product with the same component cells or transgenes as those of the product concerned is being conducted.

(2) Causal relationship

In reports of malfunctions, etc. in clinical trials, a causal relationship shall be handled as follows.

1) All cases shall be reported unless both an investigator, etc. and a sponsor rule out a causal relationship. In the case of reports by sponsor-investigators, cases other than those for which both an attending physician, etc. and a sponsor-investigator rule out a causal relationship shall be reported.

2) Overseas cases based on the information from sources other than healthcare professionals of subjects or patients, as well as their families, are not subject to reporting if the sponsor or sponsor-investigator judges that the causal relationship can be ruled out.

3) When the causal relationship with all the reported events is ruled out based on the additional information, submit the “additional report on cases not subject to reporting.” When withdrawing all reported events for other reasons, submit the “additional report on withdrawal.”

(3) Handling of applications for partial changes being prepared or pending

In cases where a clinical trial for the application for a partial change, etc. of approved product information of a regenerative medical product already approved in Japan is being conducted or all clinical trials related to the processed cells, etc. concerned have been completed, and the application for a partial change, etc. of

approved product information is being prepared or has been filed, if any measures, etc. that may affect the content of the clinical trial or application are taken for regenerative medical products with the same component cells or transgenes as those marketed in Japan, a foreign corrective action report should be submitted to the Review Planning Division, Office of Review Management, PMDA by the reporting deadline.

(4) Handling of cases related to comparator in comparative studies

The sponsor or sponsor-investigator shall report malfunctions, etc. of the comparator that is not blinded, to the company providing the comparator, and the company providing the comparator shall also report the cases of malfunctions, etc. concerned as "Post-marketing reports of malfunctions, etc." In this case, "Reporting of Adverse Reactions, etc. to Drugs, etc." (PFSB Notification No. 1002-20 of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated October 2, 2014) shall be followed for malfunctions, etc. of comparators. If the product concerned is found to be the test product after unblinding in a report from a double-blind study, make an additional report on the test product. If the product concerned is found to be the comparator, report the matter to that effect.

(5) Reporting deadline

1) For reports based on Article 275-3, Paragraph 1 or 2 of the Regulation, the reporting deadline shall be determined by counting from the day after the date on which information was obtained. If the deadline for reporting falls on a non-business day of PMDA, the next business day should be regarded as the deadline for reporting.

2) The reports based on Article 275-2, Paragraph 4 of the Regulation shall be submitted within 2 months after the end of each reporting period. If the deadline for reporting falls on a non-business day of PMDA, the next business day should be regarded as the deadline for reporting. The last annual report after approval or submission of a development discontinuation notification shall be made within 2 months from the date of approval or submission of a development discontinuation notification.

(6) Handling of mandatory reporting period

The mandatory reporting period is, in principle, the period after the submission of the first clinical trial notification for reports based on Article 275-2, Paragraph 1 of the Regulation or from the base date for reporting for reports based on Paragraph 3 of the same article, up to gaining of the approval of the investigational product or the submission of a development discontinuation notification. However, if the investigational product provider (including the approval applicant; the same applies in this section) continues to develop the product concerned after all the clinical trials by a sponsor-investigator have been completed and the completion notification or discontinuation notification has been submitted, the investigational product provider shall make reports of malfunctions, etc. in clinical trials for the product concerned or other study products until the approval or submission of a development discontinuation notification. If any malfunction, etc. occurs in an implantable investigational product after its approval, the malfunction, etc. concerned shall be

reported in a “Post-marketing report of malfunctions, etc.” If an improved product is approved based on the results of the product implanted in the clinical trial, a malfunction, etc. of the investigational product implanted that occurs after the approval shall be reported in a “Post-marketing report of malfunctions, etc.” in the same manner. For clinical trials conducted by sponsor-investigators, annual reports are not necessary if the duration of each study is less than one year.

(7) Handling of overlapping information on malfunctions, etc. when there are multiple notifiers

1) If multiple clinical trials of the test product concerned are being conducted in Japan by a different sponsor or sponsor-investigator, it is acceptable to omit overlapping reports by submitting the report of cases of malfunctions, etc. in Japan for each clinical trial to regulatory authorities. However, even in such cases, information shall be appropriately shared between the two parties.

2) The sponsor-investigator may omit overlapping reports of malfunctions, etc. in clinical trials, foreign corrective action reports, and research reports if the investigational product provider, etc. has already made a report or the sponsor-investigator has confirmed that the report is scheduled to be made to the regulatory authorities within the period specified in laws and regulations (e.g., a notice of the scheduled date of a report was received) at the time when the sponsor-investigator becomes aware of the information related to the report. In that case, both parties shall share information appropriately, and include the statement, “The reports corresponding to Attachment 6, (7), 2) of ‘Points to Consider for Reporting of Malfunctions, etc. in Clinical Trials Related to Processed Cells, etc.’ (PSEHB/MDED Notification No. 0831-11 of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020) are omitted,” in the remarks column of the clinical trial notification in advance. However, note that malfunctions, etc. that occurred in clinical trials conducted by sponsor-investigators need to be reported to the regulatory authorities. Note that this precaution does not affect the provisions of Article 39, Paragraph 2 of the Ministerial Ordinance on Good Clinical Practice for Regenerative Medical Products (MHLW Ordinance No. 89 of 2014) which require a sponsor-investigator to notify the head of the medical institution of information on malfunctions, etc. related to the study product.

3) For a regenerative medical product that has already been approved in Japan, if a clinical trial is conducted for a partial change application for indications by a party other than the party that has obtained the approval of the regenerative medical product concerned as the sponsor and the information is appropriately shared between the parties, it is acceptable for the party that has obtained approval to submit the reports of overseas cases of malfunctions, etc. However, the sponsor and the party that obtained approval should come to an agreement on the matters related to reporting of overseas cases and information sharing in advance. In this case, the sponsor shall enter the approval number of the regenerative medical product concerned in the remarks column of the clinical trial notification. The party that

obtained approval shall enter "TIKEN" in half-width alphabet characters in the "remarks" column when making post-marketing reports of malfunctions, etc. for the regenerative medical product concerned.

(8) Handling of long-term suspension of development, etc.

If development is suspended for a long time, it is possible to withhold reporting until the development is resumed, by notifying the Review Planning Division, Office of Review Management, PMDA of the situation in writing. Efforts shall be made to collect safety information even while reports are withheld, and the information concerned shall be reflected in the Investigator's Brochure, etc. and the protocol when the development is resumed. When resuming the reporting with the resumption of development, submit necessary documents to the Review Planning Division, Office of Review Management, PMDA.

1) Document notifying withholding

Prepare a document describing the following and submit it to the Review Planning Division, Office of Review Management, PMDA.

A The title should be "Notification of withholding of reports of malfunctions, etc. associated with the investigational product."

B Enter the clinical trial identification code, and the proposed generic name in parentheses.

C Enter the number of clinical trial notifications submitted and the date of the first clinical trial notification.

D Enter the proposed intended use and indications.

E Enter the development phase in which clinical trials are to be suspended.

F Specify the "reason for withholding reporting."

G State that the party withholding reporting is to "continue to make efforts to collect information on malfunctions, etc.," "report the adverse reactions, etc. collected while the development is suspended, when the development is resumed," and "contact the Review Planning Division, Office of Review Management, PMDA in advance when the development is resumed."

2) Documents to be submitted at the time of resumption of development

When the development is resumed, terminate withholding and resume the reporting of malfunctions, etc. In such cases, prepare a document writing the following and submit it to the Review Planning Division, Office of Review Management, PMDA.

A The title should be "Notification of termination of withholding reports of malfunctions, etc. associated with the investigational product" and enter the reason for withholding, withholding period, and reason for termination of withholding.

B The information collected while reports were withheld shall be submitted using Attached Forms 3 and 4 of the Director-General Notification.

C Revised or corresponding parts of the Investigator's Brochure, etc. or protocol and summary of the product application prepared based on the information collected during the withholding period

(9) Reporting of adverse reactions, etc. or malfunctions, etc. related to drugs or machines/equipment, etc. used in clinical trials of processed cells, etc.

For the scope of reporting and reporting deadlines, etc. of reports of adverse reactions, etc. or malfunctions, etc. related to drugs (study drug equivalents) or machines/equipment, etc. (study device equivalents) used in clinical trials of processed cells, etc., conform to the "Reports of Adverse Reactions, etc. in Clinical Trials to Pharmaceuticals and Medical Devices Agency" (PSEHB Notification No. 0831-8 of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020), "Post-marketing Reports of Adverse Reactions, etc. and Reports of Adverse Reactions, etc. in Clinical Trials According to E2B (R3) Implementation Guide" (PSEHB/PED Notification No. 0831-12, PSEHB/PSD Notification No. 0831-3 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020), "Reports of Adverse Reactions, etc. in Clinical Trials by Sponsor-investigators" (PSEHB/PED Notification No. 0831-13 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020), "Reports of Malfunctions, etc. in Clinical Trials Related to Machines/Equipment to Pharmaceuticals and Medical Devices Agency" (PSEHB Notification No. 0831-9 of the Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020), and "Points to Consider for Reporting of Malfunctions, etc. in Clinical Trials Related to Machines/Equipment to Pharmaceuticals and Medical Devices Agency" (PSEHB/MDED Notification No. 0831-10 of the Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated August 31, 2020). The reporting method (including report forms) shall be in accordance with the method for reporting malfunctions, etc. related to study products shown in the Director-General Notification and this notification.

(10) Other

1) In the case of emergency that requires discontinuation of the clinical trial, the first report should be sent by fax or e-mail after contacting the Review Planning Division, Office of Review Management, PMDA by phone in advance. In this case, the date on which the report concerned is received is regarded as the date of the report, and a formal report shall be made at a later date. The first report concerned should not be included in the number of reports to PMDA. When sending a fax (e-mail), describe the currently available information in the applicable items in Attached Form 1 of the Director-General Notification, state "Report by fax (e-mail)/To the Review Planning Division, Office of Review Management, PMDA," and send it by fax (e-mail).

2) Even if information for sufficient description or evaluation necessary for a case report cannot be obtained by the deadline specified in Article 275-3, Paragraph 1,

Items 1 to 3 and Paragraph 2, Items 1 to 3 of the Regulation, the first report should be submitted within the deadline as long as information on an event that can be judged to be serious and unexpected malfunction, etc. (status of health damage in subjects, etc. or status of malfunctions, etc. of the test product) has been obtained, in light of the purpose of expedited reporting.

3) Reporting shall be done for each clinical trial identification code.
4) In the case of joint development, report malfunctions, etc. in joint names, in principle.
5) If there are any submission data, submit one copy. In principle, MedWatch report forms and other safety information, etc. reported to medical institutions do not need to be attached. However, the presentation or submission may be requested as necessary.